# BRIEF COMMUNICATIONS

## SHORT-TERM NEUROPSYCHOLOGIC DIFFERENCES AFTER NORMOTHERMIC VERSUS HYPOTHERMIC CARDIOPULMONARY BYPASS

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Despite many improvements in the practice of cardiac surgery, anesthesiology, and perfusion technology, discrete central nervous system dysfunctions are still observed in a number of patients undergoing cardiopulmonary bypass (CPB), although serious complications have become rare. The traditional form of cerebral protection in CPB has been hypothermia. As more cardiac surgery units apply normothermic CPB, there is some concern that this could lead to a higher incidence of central nervous system dysfunctions. The influence of perfusion temperature on neuropsychologic outcome has been examined in some studies[1-4] with inconsistent results; these studies failed to demonstrate a clear neuroprotective effect of hypothermia. The aim of this prospective, randomized study was to evaluate the short-term influence of systemic temperature during CPB on early postoperative cognitive, psychomotor, and emotional states.

**Methods.** After the local ethics committee had approved the study and informed consent had been obtained from each patient, 30 male patients undergoing primary isolated coronary artery bypass grafting were randomly assigned to either mildly hypothermic (30° C, $n = 15$) or normothermic (36.5° C, $n = 15$) CPB. All patients were operated on by the same surgeon. Patients with an unstable cardiac disease, previous neurologic illness, impaired renal function, or age younger than 55 or older than 75 years did not participate in this study.

Preoperative data were collected with standard clinical measures, and the general level of cardiac impairment was described by New York Heart Association functional classification and the Cleveland Clinic score. Perioperative data included crossclamp duration, CPB duration, duration of the operation, and the number of bypass grafts. During CPB, the mean arterial pressure was recorded every 5 minutes and the venous oxygen saturation levels were assessed every 20 minutes. The total time during which mean arterial pressure was less than 50 mm Hg was also determined.

The anesthetic protocol consisted of premedication with 2 mg flunitrazepam and 300 μg clonidine. Anesthesia was induced with propofol (1 mg/kg), sufentanil (25 μg), and pancuronium bromide (0.2 mg/kg). After tracheal intubation, anesthesia was maintained with intravenous infusions of propofol and sufentanil. (All drugs are cited by generic names.) Alpha-stat acid-base management was applied during the operation. In the intensive care unit the patients received continuous infusions of propofol (100 mg/hour) until extubation. No attempt was made to standardize the postoperative administration of opioid agents, but individual use and dosage were assessed.

A heart-lung machine (Stöckert Instrumente, Munich, Germany) with centrifugal pump (Biomedicus; Medtronic, Inc., Minneapolis, Minn.), membrane oxygenator (HF 5701; Bard Cardiopulmonary Division, Haverhill, Mass.), and arterial line filter (CBM 4.0; Medtronic) were used for CPB. The extracorporeal circuit was primed with 2200 ml lactated Ringer's solution and 5000 U heparin. Nonpulsatile flows of at least 1.7 L/min/$m^2$ were used at hypothermia and were not lower than 2.0 L/min/$m^2$ during normothermia. Cardiac arrest was induced with antegrade administration (150 ml/min for 4 minutes) of cold (4° C) colloid cardioplegic solution (Fresenius, Bad Homburg, Germany) and was followed by infusions of 300 ml every 25 minutes. After institution of CPB, patients in the hypothermia group were cooled to 28.5° C (blood temperature) during the first 20 minutes and then raised again to a steady level of 30.5° C. Postcardiotomy rewarming was managed in three successive periods: 10 minutes at 35° C, 10 minutes at 36.5° C, and then stabilization at 37.4° C blood temperature. In the normothermic group the maximal blood temperature was 37.5° C. The nasopharyngeal temperatures of both treatment groups are shown in Table I.

Because memory functioning, attention, and psychomotor performance are often impaired after cardiac operations and because of the physical limitations of patients, the following tests were applied before the operation and on the first and second day after the operation: (1) Syndrom-Kurztest (SKT),[5] a brief neuropsychologic test

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Received for publication Feb. 9, 1998; accepted for publication Feb. 17, 1998.

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J Thorac Cardiovasc Surg 1998;116:350-3



0022-5223/98 $5.00 + 0 **12/54/89810**

**Table I.** *Patient characteristics and perioperative data*

| *Variable* | *Hypothermic group (n = 15)* | *Normothermic group (n = 15)* | *p* |
|---|---|---|---|
| Nasopharyngeal temperature (°C) | 32.9 ± 0.7 | 36.5 ± 0.5 | 0.00 |
| Age (yr) | 64.5 ± 7.3 | 62.5 ± 5.3 | 0.41 |
| NYHA | | | |
| I and II | 13 | 12 | 1.0 |
| III and IV | 2 | 3 | |
| Cleveland Clinic score | | | |
| 0 and 1 | 12 | 12 | 1.0 |
| 2 and 3 | 3 | 3 | |
| LVEF (%) | 78.1 ± 18.3 | 68.8 ± 22.6 | 0.23 |
| No. of bypass grafts | 3.1 ± 0.6 | 3.0 ± 0.4 | 0.49 |
| CPB time (min) | 98.5 ± 19.9 | 90.2 ± 14.1 | 0.20 |
| Aortic crossclamp time (min) | 68.4 ± 16.4 | 62.8 ± 16.1 | 0.35 |
| Duration of operation (min) | 214.3 ± 28.1 | 192 ± 20.5 | 0.01 |
| Duration of postoperative intubation (hr) | 9.0 ± 2.5 | 7.4 ± 2.9 | 0.11 |
| MAP (mm Hg) | 56.0 ± 4.2 | 53.2 ± 5.9 | 0.15 |
| Duration of MAP < 50 mm Hg during CPB (min) | 18.7 ± 10.6 | 24.5 ± 15.9 | 0.25 |
| $SvO_2$ during CPB (%) | 74.8 ± 3.6 | 73.3 ± 3.3 | 0.23 |
| Piritramid (mg/kg) | 0.38 ± 0.14 | 0.41 ± 0.14 | 0.53 |

Data are mean ± standard deviation. *NYHA,* New York Heart Association functional class; *LVEF*, left ventricular ejection fraction; *MAP,* mean arterial pressure; *$SVo_2$,* venous oxygen saturation.

with alternate forms to assess attention and memory dysfunctions;(2) finger tapping (from the Halstead-Reitan test battery[6]) to test psychomotor speed, (3) the Spielberger State Trait Anxiety Inventory [6]; (4) the Profile of Mood States,[6] with the subscores Dejection, Fatigue, Vigor-activity, and Hostility, to measure subjective changes in mood; and (5) a numeric rating scale to assess the intensity of pain. The examiner and subjects were unaware of the body temperature during CPB.

The statistical analyses were performed by means of Statistical Package for the Social Sciences for Windows software (version 6.0; SPSS, Inc., Carey, N.C.). Group differences in perioperative data were evaluated by unpaired *t* test or $\chi^2$ test. Differences in the psychologic test scores between the two groups and the three test occasions were tested by a two-way analysis of variance with repeated measurements in the second (times) factor and by subsequent a posteriori Scheffé tests. An analysis of regression was used to evaluate possible influences of mood and other factors on postoperative cognitive function.

**Results.** Patient characteristics and perioperative data except for duration of the procedure were similar between the two groups (Table I). Only the postoperative intubation time had a significant general worsening effect on cognitive functions in both groups, as revealed by regression analysis. The analysis of variance of the neuropsychologic performance indicated significant main and interaction effects. Both groups started from a similar preoperative SKT level and then had a significant postoperative deterioration (Fig. 1), but on the first postoperative day the patients who had undergone normothermic CPB showed significantly less impairment than did those who had undergone hypothermic CPB.

On the second day after the operation both groups had improved slightly, and the group difference was no longer significant. There was thus only a short-lived effect of intraoperative temperature. Analysis of tapping indicated a significant effect of time, no interaction, and a group effect only for the preferred hand. Post hoc analysis confirmed that both groups decreased in psychomotor speed after the operation. Patients in the normothermic group exhibited better performances for the preferred hand on all three test occasions, including before the operation, despite random assignment to groups. The analysis of intensity of pain indicated a significant time and interaction effect. In the cooled group the pain intensity increased on the first postoperative day, dropping back on the second day but still remaining at a higher level than before the operation (Fig. 1). In contrast, patients in the normothermic group showed no significant daily variation in the intensity of pain. Analysis of regression indicated no significant influence of pain on SKT performance. No group differences were found in the emotional state results. The Vigor-activity subscores of the Profile of Mood States decreased and the Fatigue subscore increased from the preoperative to postoperative period in both groups, a rather trivial result.

**Discussion.** In accordance with previous studies, we were not able to find a neuroprotective effect of hypothermia on neuropsychologic performance after coronary artery bypass grafting with CPB.[1-3] On the contrary, patients in the normothermic group showed lesser postoperative attention and memory impairments than did those in the hypothermic group, mainly on the first postoperative day. It is difficult to compare our results with those of other studies because of the time of testing

The Journal of Thoracic and
Cardiovascular Surgery
August 1998

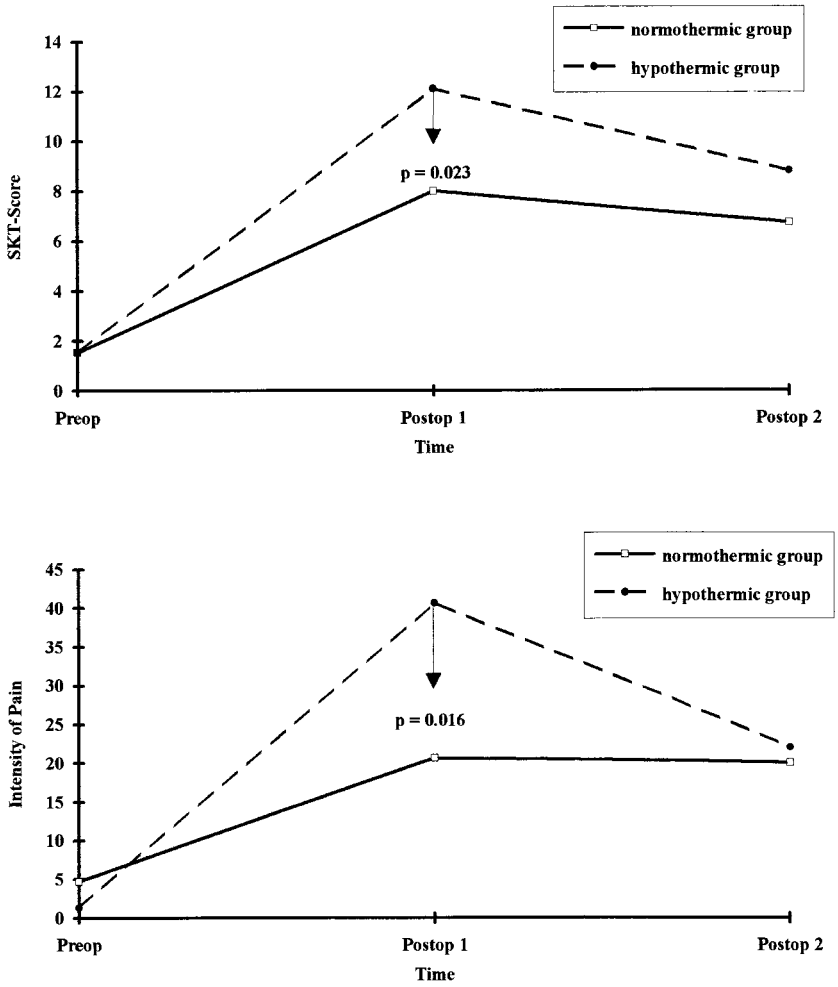


**Fig. 1.** Variation of performance in SKT (a higher value in SKT demonstrates a lower performance) and intensity of pain. Data are mean values. *Postop 1,* First postoperative day; *Postop 2,* second postoperative day.

and the management in perfusion temperature. In some studies patients undergoing normothermic CPB were actively warmed,[3, 4] and in others the temperature management strategies varied considerably.[1, 2] Nevertheless, this study supports the results of Wong and colleagues,[1] who reported that patients who underwent normothermic CPB tended to perform better on neuropsychologic testing on the fifth postoperative day. On extension of the study and at 3-month follow-up, however, this difference was no longer found.[2] In a study by Mora and associates[3] no differences were found at all. On the other hand, Regragui and coworkers[4] reported a benefit 6 weeks after the operation for patients who underwent hypothermic CPB.

A factor that may have contributed to our finding for patients who underwent normothermic CPB is their shorter duration of intubation, which did not reach significant statistical group difference but was found to have a general impact on cognitive outcome. The higher intensity of pain in the hypothermic group did not explain our results, and the dosages of analgesic were equal in the two groups. One speculative factor in the lower neuropsychologic performance of the hypothermic group is the possible higher risk of gas embolic load during rewarming,[7] because cerebral microemboli are thought to be a possible cause of cognitive deficits. This possible explanation needs further studies, as does the lower intensity of postoperative pain in the normothermic group, reported here for the first time to our knowledge. At least for the short postoperative term, our results do not suggest any neuropsychologic contraindications to the observed trend in cardiac surgery favoring normothermic CPB.

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